

REMARKS

The present amendment is provided in addition to the amendment submitted October 20, 2006, and Applicants respectfully request that both amendments be entered. Following entry of the amendment submitted on October 20, 2006, claims 71-87 are pending and under examination in the Application. By the present amendment, claim 88 is added to specifically recite one embodiment of the present invention. Claim 88 is identical to claim 86, except that it recites vincristine instead of vincristine sulfate. Support for this claim is provided throughout the instant application as filed, including, *e.g.*, page 11, lines 13-17, and it does not constitute new matter. Claim 87 has been amended to recite additional features of one embodiment of the present invention. Support for this amendment is provided throughout the instant application as filed, and it does not constitute new matter. Specifically, support for vincristine in the range of 1 mg/ml to 5 mg/ml is provided on page 18, lines 10-12, which recites concentrations of, *e.g.*, 1 mg/ml, 2 mg/ml, and 5 mg/ml.

As enunciated in the M.P.E.P. §2163.05, with respect to numerical range limitations, analysis of whether the range is supported by the application must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement. Applicants submit that this situation is analogous to the present situation, in which the instant application specifically discloses representative concentrations of 1 mg/ml, 2 mg/ml, and 5 mg/ml. Clearly, one skilled in the art would consider the claimed range of 1 mg/ml to 5 mg/ml inherently supported by the instant application.

In light of the above amendments, claims 71, 73, 74, 76-81 and 83 are canceled, and claims 75, 82, 84, and 85 are amended to maintain proper dependency. Accordingly, claims 75, 82, and 84-88 are pending and under examination following entry of the present amendment. It should also be noted that the above amendments are made without prejudice to prosecution of any subject matter removed or modified by amendment in a related divisional, continuation or continuation-in-part application.

The following remarks are provided in response to the Office Action mailed July 20, 2006 and in addition to the remarks provided in the amendment submitted on October 20, 2006.

Examiner Interview

Applicants wish to thank the Examiner for conducting a personal interview with Dr. Thomas D. Madden of Inex Pharmaceuticals Corp., an assignee of the instant application, and Dr. Carol D. Laherty, Applicants' representative in the instant application. It is Applicants' understanding that the Examiner believes that claim 86 is allowable in light of the discussions that took place at the interview. In addition, Examiner Kishore indicated that a similar claim reciting "vincristine" as opposed to "vincristine sulfate" would likely also be allowable. Applicants also note that the Examiner indicated that certain limitations present in claim 86 may likely be broadened and still retain allowability.

In accordance with the discussions at the interview, by the present amendment, Applicants have retained claim 86 without amendment and have added new claim 88, which is identical to claim 86, except that it recites "vincristine" instead of "vincristine sulfate." As noted in a further Declaration of Dr. Thomas D. Madden, submitted with this Amendment, the instability of vincristine in citrate buffer should not be dependent on the salt form as full dissociation will occur in solution. It is Applicants' understanding that these claims will be found allowable, in light of the understanding reached at the interview. In addition, Applicants have amended claim 87 to incorporate additional features of the presently claimed kits that clearly render them non-obvious over the cited prior art. Applicants further note that the remaining claims are limited to vincristine and recite that the liposomes are present in citrate buffer.

Applicants further note that commercially available vincristine sulfate, *e.g.*, Vincasar®, is provided in 100 mg/ml mannitol with a pH range from 3.5 to 5.5.

Rejections Under 35 U.S.C. §103

Claims 71-86 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentably obvious over one or more references, including (1) Webb (U.S. Patent No. 5,741,516); Webb in combination with Mehlhorn (U.S. Patent No. 5,762,957); (3) Mehlhorn in view of Webb, and (4) Webb by itself or in combination with Mehlhorn or *vice versa*, further in view of Lenk (U.S. Patent No. 5,262,168). Applicants traverse these bases of rejection and submit that the claimed kits are not obvious over these combinations of references.

Further to the remarks provided in the amendment submitted on October 20, 2006, Applicants provide with this amendment additional evidence of the non-obviousness of the presently claimed kits over the cited references, alone or in any combination. In particular, Applicants submit with the present amendment a further Declaration of Dr. Thomas D. Madden, which emphasizes the surprising advantages of the presently claimed kits and emphasizes the non-obviousness of the presently claimed kits over the kits described by Mehlhorn. This Declaration also provides additional experimental data demonstrating that the presently claimed kits are not obvious over the cited prior art.

Applicants have submitted data in a previous Declaration by Dr. Thomas D. Madden (October 20, 2006) showing that vincristine is surprisingly unstable when loaded into liposomes using a citrate buffer (pH 4.0 - 4.5), which is preferred for loading liposomes and is present in the liposome interior according to the present invention. Indeed, the liposome encapsulated vincristine failed USP limits for impurities after less than six months storage at 2-8°, which is unacceptable for a commercial product. This finding was contrary to the expected result, since the chemical stability of vincristine is well-established, and it has been shown that vincristine has optimal stability at pH 4.0 to pH 5.0 (Vendrig *et al.*, International Journal of Pharmaceutics, 50 (1989) 189-196).

In the presently submitted Declaration, Dr. Madden provides additional data showing that vincristine is also unstable in citrate buffer alone. These findings are relevant to the Examiner's suggestion that the presently claimed kits are obvious in light of Mehlhorn, alone or in combination with Webb, since they demonstrate that the kits described by Mehlhorn are also unsuitable for vincristine. Accordingly, the presently claimed kits, wherein vincristine is provided in a separate vial is not obvious over Mehlhorn, alone or in combination with Webb.

Mehlhorn describes a kit containing two vials, *i.e.*, a liposome vial and a buffer vial. According to Mehlhorn, the drug is present in one of these two vials (column 3, lines 40-42). Mehlhorn makes absolutely no reference to the possibility that the drug is provided in a separate vial. However, while the two-vial kit described by Mehlhorn may be appropriate for many drugs, it is not suitable for vincristine, due to the surprising instability of vincristine in the citrate buffer used to load drug into the liposomes and present in the liposome vial (see presently submitted Declaration of Dr. Thomas D. Madden). In the context of kits for preparing liposomal vincristine, according to Mehlhorn, vincristine must necessarily be present in either the liposome vial comprising citrate buffer, where it would be unacceptably unstable, or the basic sodium phosphate buffer, where it would also be unstable. Thus, the kit configurations described by Mehlhorn are not suitable for liposomal vincristine. Furthermore, neither Mehlhorn nor Webb provide any teaching or suggestion to provide vincristine in a separate vial from the liposomes and the buffer in a kit.

In light of the above amendments and remarks, as well as those submitted on October 20, 2006, Applicants submit that the presently claimed kits are not obvious over the cited references, alone or in any combination. More specifically, Applicants submit that the presently claimed kits offer surprising advantages over the prior art, and further that the prior art fails to describe each element of the claimed kits or provide motivation to combine or modify the teachings of the prior art to achieve the presently claimed kits. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

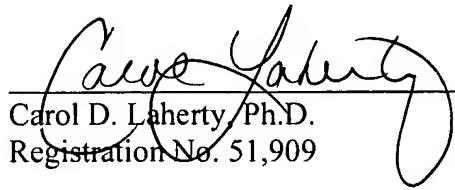
The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Application No. 10/782,738
Supplemental Reply to Office Action dated July 20, 2006

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosure:

Declaration of Thomas D. Madden, Ph.D.

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